INTER-INDIVIDUAL DIFFERENCES IN ASSOCIATIVE MEMORY:

Structural and functional brain correlates and genetic modulators

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Structural and functional brain correlates and genetic modulators

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Für meine Eltern.

ABSTRACT

Our memory for personal experiences (e.g., the first day at school) is termed episodic memory. This form of memory involves the recollection of single information as well as the connection between these pieces of information (e.g., what happened when, and where), referred to as associative memory. Associative memory declines markedly in aging; however, some individuals have proficient associative memory even until late life. These individual differences in associative-memory performance are also observable at younger ages. The underlying sources of these individual differences remain unclear. In this thesis, we aimed to identify the neural underpinnings of individual differences in associative memory, with special regard to brain structure, function, and neurochemistry.

In the first part of the thesis, we investigated structural brain correlates of and dopaminergic contributions to associative memory in healthy older adults (studies I and II). In study I, we examined the relationship between regional gray-matter volume and associative memory. Individuals with better associative memory had larger gray-matter volume in dorsolateral and ventrolateral prefrontal cortex, suggesting that organizational and strategic processes distinguish older adults with good from those with poor associative memory. In study II, we examined the influence of dopamine (DA) receptor genes on item and associative memory. Individuals with less beneficial DA genotypes performed worse in the associative-memory task compared with carriers of more beneficial genotypes. Because no such group differences were found with regard to item memory, this suggests that dopaminergic neuromodulation is particularly important for associative memory in older adults.

In the second part of the thesis, we examined in a sample of younger adults how different task instructions influence associative encoding, as well as the structural-functional coupling between task-relevant brain regions during associative-memory formation (studies III and IV). In study III, we investigated the effect of encoding instruction on associative memory. Specifically, we examined functional brain correlates of intentional and incidental encoding and demonstrated differential involvement of anterior hippocampus in intentional relative to incidental associative encoding. This suggests that the intent to remember associative information triggers a binding process accomplished by this brain region. Finally, in study IV we explored how gray-matter volume is associated with brain activity during associative-memory formation. We observed a relationship between gray-matter volume in the medial-temporal lobe (MTL) and functional brain activity in the inferior frontal gyrus (IFG). Importantly, this structure-function coupling correlated with performance, such that younger individuals with a stronger MTL-IFG coupling had better associative memory.

Collectively, these four studies show that the neural underpinnings of individual differences in associative memory are many-faceted, interacting with each other and vary with regard to age and specific features of the associative task.

List of scientific papers

This thesis is based on the following publications, which are referred to in the text by their roman numerals (study I–IV).

I. **Becker, N.**, Laukka, E. J., Kalpouzos, G., Naveh-Benjamin, M., Bäckman, L., & Brehmer, Y. (2015). Structural brain correlates of associative memory in older adults. *Neuroimage, 118*, 146-153.

II. Papenberg, G., **Becker, N.**, Ferencz, B., Naveh-Benjamin, M., Laukka E. J., Bäckman, L., & Brehmer, Y. (2017). Dopamine receptor genes modulate associative memory in old age. *Journal of Cognitive Neuroscience, 29*, 245-253.

III. **Becker, N.**, Kalpouzos, G., Persson, J., Laukka, E. J., & Brehmer, Y. (2017). Differential effects of encoding instructions on brain activity patterns of item and associative memory. *Journal of Cognitive Neuroscience, 29*, 545-559.

IV. **Becker, N.**, Kalpouzos, G., Salami, A., Laukka, E. J., & Brehmer, Y. (submitted for publication). Structure-function associations of successful associative encoding.

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LIST OF ABBREVIATIONS

APOE	Apolipoprotein E
BA	Brodmann area
BIN1	Bridging integrator 1
BOLD	Blood-oxygen-level dependent
CLU	Clusterin
COMT	Catechol-O-methyltransferase
DA	Dopamine
DARTEL	Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra
DNA	Deoxyribonucleic acid
DRD1-3	Dopamine receptor D1-3
FWHM	Fullwidth-half-maximum
ICA	Independent component analysis
GLM	General linear model
IFG	Inferior frontal gyrus
jICA	Joint independent component analysis
MCI	Mild cognitive impairment
MNI	Montreal Neurological Institute
MRI	Magnetic resonance imaging
MTL	Medial temporal lobes
PET	Positron-emission tomography
PFC	Prefrontal cortex
PICALM	Phosphatidylinositol binding clathrin assembly protein
SNP	Single-nucleotide polymorphisms
VBM	Voxel-based morphometry

INTRODUCTION

Memory declines in aging, which impacts older adults' everyday lives, their independence, and can lead to depressive symptoms (Reid & Maclullich, 2006). Especially the decline of associative memory, for example to remember a face-name combination, where one left the car keys, or which medication to take at which time, influences our everyday life. Moreover, there are pronounced individual differences in associative memory, leaving some adults with relatively intact, and others with severely deficient associative memory. To date, the underlying neural sources for this heterogeneity are unclear. Studies have shown the potential for cognitive improvement across the life span, i.e., even at older ages, adults are able to enhance their cognitive abilities (e.g., through memory interventions) by increasing their potential to use cognitive resources (Nyberg et al., 2003). However, to generate efficient and individualized interventions for older adults, factors determining maintenance or reduction of associative memory need to be identified. Potential sources for such individual differences are structural, functional, and neurochemical differences in the brain. Understanding how these brain factors are related to associative memory will help understanding which processes underlie successful associative operations. This knowledge might clear a way to develop individualized and efficient interventions to maintain individuals' memory functions even in later life.

Associative Memory

The acquisition and retrieval of personal experiences is central for our life. This form of memory is termed episodic memory, the conscious remembrance of events that are situated in time and place (Tulving, 1972). Episodes usually occur as complex entities composed of various single pieces of information that need to be linked together. Consider for example your last birthday party and you will most likely remember the people attending, their names, the location, and food, among other details. The example illustrates that episodic memory typically entails two forms of memory: the recollection of single items (e.g., remembering a name), and the relationship among those items (e.g., linking a name to a specific face; Chalfonte & Johnson, 1996; Treisman, 1996; Davachi, 2006; Zimmer et al., 2006). The latter variety is commonly referred to as associative memory. This is a highly important ability, as memory for the relationships between single units allows us to adapt our behavior in future events and novel contexts. Generally, both younger and older adults perform better in item compared with associative memory tests (Naveh-Benjamin, 2000; Kamp & Zimmer, 2015), and this effect has consistently been observed with numerous types of stimuli

(e.g., words, faces, names; Old & Naveh-Benjamin, 2008). A recurrent observation in aging is that the difference in item and associative-memory performance is disproportionally larger in older compared with younger adults. This age-related decline in associative memory is discussed in more detail in the following.

Associative Memory in Older Adults

Aging is associated with decline of many cognitive functions. Longitudinal studies show that episodic memory remains stable until the age of 60 before it starts to deteriorate (Rönnlund et al., 2005). According to the *associative-deficit hypothesis* (Naveh-Benjamin, 2000), this decline in episodic memory largely reflects a deficiency in associative memory. More precisely, while older adults show marked impairment in associative memory, their memory for single information may remain relatively intact (Figure 1; Schacter et al., 1991; Naveh-Benjamin, 2000). In a meta-analysis, Old and Naveh-Benjamin (2008) showed that the age-related associative deficit occurs with different stimulus materials (i.e., verbal and non-verbal) and generalizes across a variety of bindings, such as links between two items (inter-item associations), an item and its features (intra-item associations), an item and its context or spatial location, or two pieces of contextual information. This indicates that the relative inability to form and retrieve associative information appears to be highly robust in old age, with one exception to the rule: Different encoding instructions (incidental vs. intentional) have been shown to affect the associative-memory deficit in older adults (Naveh-Benjamin et al., 2007; Naveh-Benjamin et al., 2009). When encoding instructions are incidental, individuals are not aware of a subsequent memory task. In contrast, under intentional encoding instructions individuals know that their memory will later be tested and therefore may try to memorize the information. Naveh-Benjamin et al. (2009) demonstrated that, under incidental encoding instructions, older adults performed uniformly worse than younger adults in both item and associative memory tasks. The age-related associative deficit, however, was found only under intentional encoding instructions.

Moreover, the age-related associative deficit seems to emerge as older adults are more susceptible to false alarms in recognition of associations than younger adults (i.e., remember episodes that did not occur; Jacoby & Rhodes, 2006; Bender et al., 2010; Fandakova et al., 2013). In fact, studies reported a stronger association between age and false endorsement of rearranged associations (i.e., novel configurations of already seen items) than between age and failure to recognize intact associations (Bender et al., 2010). Such results have been obtained in associative-

memory paradigms with word pairs (Shing et al., 2009; Bender et al., 2010) and face-name associations (Naveh-Benjamin et al., 2009).

Thus, there are three common observations: (1) item memory is generally higher compared with associative-memory performance in both younger and older adults, and (2) the difference between item and associative-memory performance is magnified in aging, which (3) relates to an increase of false alarms in older adults. From these observations, we can assume that there are different cognitive processes that underlie the two forms of episodic memory. Suggestions for what these processes might be and how they are differentially affected in aging will be discussed next.

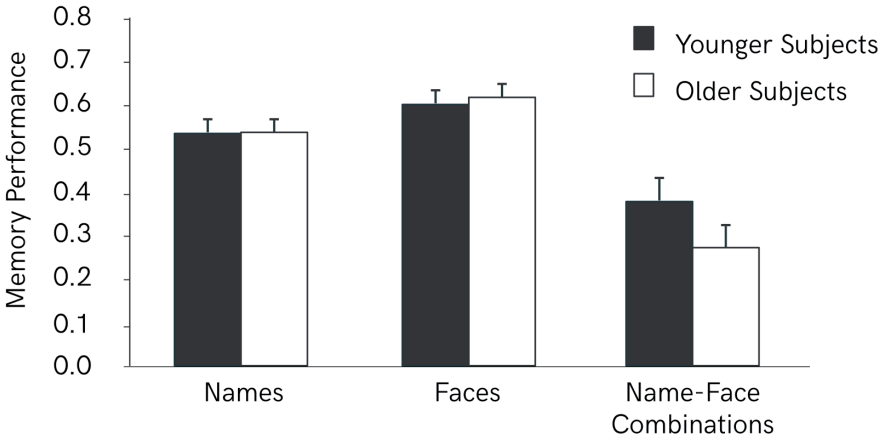

Figure 1. Test of the associative-deficit hypothesis. Memory performance for younger and older adults in two single item (name, face) and an associative (name-face combination) recognition test after intentional encoding. While older adults' item-memory performance is comparable to that of younger adults, they differ significantly with regard to associative memory. Error bars represent standard errors around the means. Adapted from Naveh-Benjamin et al. (2009).

Processes Underlying Item and Associative Memory

While a variety of studies have provided support for a distinction between item and associative memory, the difference in performance brings into question which processes underlie the formation and retrieval of associative information and how these are distinct from those involved in item memory.

Two processes that may account for the apparent difference in item and associative memory in younger and older adults are described in the *dual-process theory*. According to this theory, memory retrieval relies on two qualitatively dissociable processes, namely familiarity and recollection (Yonelinas, 1994). Whereas familiarity involves a less effortful sense of knowing, recollection requires a more conscious form of memory for contextual detail and the target item with which the context was associated. Therefore, recognition of associative information primarily relies on recollection, while single-item recognition can be based on familiarity (Yonelinas, 1997). With regard to aging, one widely held view is that aging affects familiarity relatively little, but has a large detrimental effect on recollection (Jennings

& Jacoby, 1993, 1997; Fandakova et al., 2015). Therefore, item memory declines less in older adults than associative memory. Similarly, the observed increase in false memories might be related to a general impairment in remembering the source of an episode due to a decrease in recollection, which makes older adults more likely to depend on familiarity. In other words, older adults might be less able to counter an increase in familiarity of a repeated item with recollection, making them more vulnerable to false memories (Jacoby & Rhodes, 2006).

Shing et al. (2008) conceptualized episodic-memory functioning using the *two-component framework of episodic memory*. According to this framework, episodic memory is driven by two interacting components, *associative* and *strategic*. The *associative component* refers to binding mechanisms during encoding, storage, and retrieval that link different aspects of an event into a cohesive memory trace. The *strategic component* refers to the organization and manipulation of elements in a memory episode through semantic knowledge, and relational elaboration of element features during encoding, storage, and retrieval. In general, proficient item memory requires less binding and less cognitive control, while associative memory puts higher demands on both the associative and strategic component. With regard to aging, associative and strategic components are suggested to be well functioning in younger adults (e.g., younger adults spontaneously display strategic behavior), but both undergo senescent decline (Cowan et al., 2006; Brehmer et al., 2007; Kirchhoff et al., 2014). The disproportionate difference in performance between item and associative memory in older compared with younger adults might hence stem from decline in both the associative and the strategic component.

In line with this view, one theoretical view proposes an *associative deficit* to account for age-related difficulties in associative memory. More precisely, age-related differences in associative memory may occur because older adults have problems in linking or integrating separate elements of an episode (Chalfonte & Johnson, 1996; Naveh-Benjamin, 2000). Evidence for such a binding deficit comes from training studies, in which older adults' memory performance relative to that of younger adults and children did not improve much after practice of a mnemonic strategy. These findings supported the idea that, because of decline in associative-binding abilities, older adults cannot further improve their memory performance, even after being provided with an effective memory strategy (Brehmer et al., 2007; Shing et al., 2008). Further support for this notion comes from studies that investigated feature binding with change-detection paradigms (Luck & Vogel, 1997). Findings showed larger age-related

differences in the ability to detect a change in a feature combination (e.g., different object and location) relative to a change in an individual feature (e.g., a different object; Mitchell et al., 2000; Cowan et al., 2006).

The *strategic deficit* view, on the other hand, states that older adults show a more general deficiency in using cognitive control processes that accounts for age-related deficits in associative memory (Giovanello & Schacter, 2012). Attempts to identify strategic and control mechanisms that regulate changes in associative-memory functioning evidently attributed age-related differences at encoding to production deficiencies. More precisely, older adults show deficits in self-initiating and producing effective, deep processing strategies relative to younger adults (Craik et al., 1983; Craik & Dirkx, 1992), such as the production of mediators (e.g., imagery or sentence generation to bind two items). Similarly, when retrieving associative information, older adults show deficiencies in using these strategies as effectively as younger adults (Dunlosky & Hertzog, 1998), involving deficits in the accessibility of associative mediators (after being able to produce them; Dunlosky et al., 2005; Hertzog et al., 2013), as well as deficits in recall-to-reject or inhibitory processes (Rotello & Heit, 2000; Cohn et al., 2008). This is supported by the observation that the associative-memory deficit becomes apparent under intentional encoding instructions, as intentional associative encoding requires strategic processes that decline in older adults (Naveh-Benjamin et al., 2009). Thus, providing older participants with strategies during encoding and retrieval significantly decreases the age-related associative deficit (Naveh-Benjamin et al., 2007).

Along these lines, evidence suggests that the propensity to false memories increases in aging due to faulty memory monitoring, i.e., the evaluation and control of information according to task goals and decision criteria (Gazzaley et al., 2005; Fandakova et al., 2013). However, only few studies have managed to experimentally disentangle associative and strategic processes (see Fandakova et al., 2013) and more work is needed to understand their relative contribution to individual differences in associative memory in aging.

The different processes described above may explain why younger and older adults perform worse in associative compared with item memory tasks, and why this difference increases in aging. However, another observation in associative-memory studies is that there are substantial between-person differences in performance (Figure 2), and that these individual differences are much larger than those typically observed in item memory. These individual differences in associative memory in younger and older adults are at the heart of this thesis.

Individual Differences in Associative Memory

Individuals differ substantially in episodic memory (Morse, 1993; Christensen et al., 1999; Wilson et al., 2002; Lindenberger, 2014), yet individual differences in associative memory seem to be much more pronounced than those observed in item memory (Nyberg et al., 2003; Brehmer et al., 2007; Fandakova et al., 2015). However, why difficulties in associative memory are more pronounced in some individuals than in others, and the conditions under which large individual differences occur, have not been studied in detail.

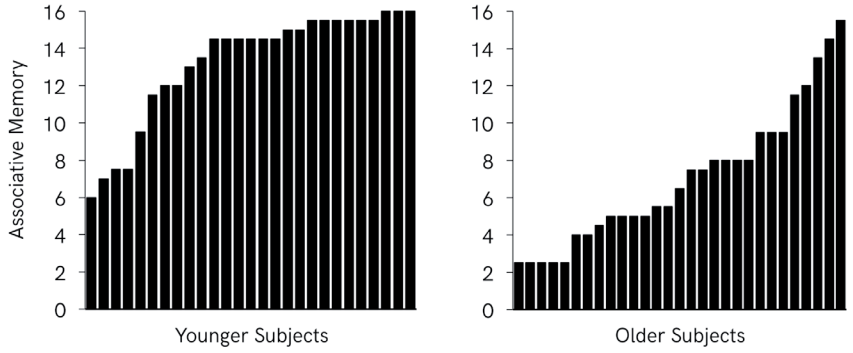

Figure 2. Illustration of individual differences in associative memory in older adults. Each bar represents associative-memory performance of a single individual. Younger adults generally perform at high levels. Older adults' performance varies substantially across individuals, with some performing at very low levels and others at levels comparable to younger adults. Data from Brehmer et al. (2007)

To date, studies have not investigated behaviorally what differs between younger adults with good and those with poor associative memory. In older adults, individual differences in associative memory have received more attention. Initially, studies that reported large inter-individual differences in associative memory did not find any cognitive or demographic variables to account for this variability, including general cognitive ability, perceptual speed, verbal knowledge, age, and educational level (Nyberg et al., 2003; Jones et al., 2006). In two other studies, variability in associative memory was related to hypertension, response bias, working-memory capacity, meta-memory, and strategy use (Bender et al., 2010; Bender & Raz, 2012). In line with a general increase of false memories in older adults, studies reported a considerable amount of variability in associative memory, especially in terms of incorrectly endorsing rearranged associations, while only small individual differences were found in older individuals' abilities in correctly detecting correct associations (Bender et al., 2010; Fandakova et al., 2015).

While the studies mentioned above have tried to relate primarily cognitive factors to individual differences in associative memory, another way to assess what factors could account for these differences is to relate performance to individual differences in brain structure and function. The core of this thesis is to

investigate neural correlates of individual variability in associative memory. The main brain-related factors examined are described in the next subsection.

Brain-Related Correlates of Associative Memory

Generally, episodic memory depends on large-scale brain networks that include the parietal cortex, the MTL, and the lateral PFC (Nyberg et al., 2000; Rugg et al., 2002; Simons & Spiers, 2003; Salami et al., 2012). In this thesis, I will focus especially on the MTL and lateral PFC. The MTL consists of a structure called the hippocampus, which is surrounded by the entorhinal, perirhinal, and parahippocampal cortices. The hippocampus entails a unique and rather automatic function to bind single pieces of information into memory traces. It receives input from perirhinal and parahippocampal areas, brain regions that are primarily involved in item memory (Figure 3; Davachi, 2006).

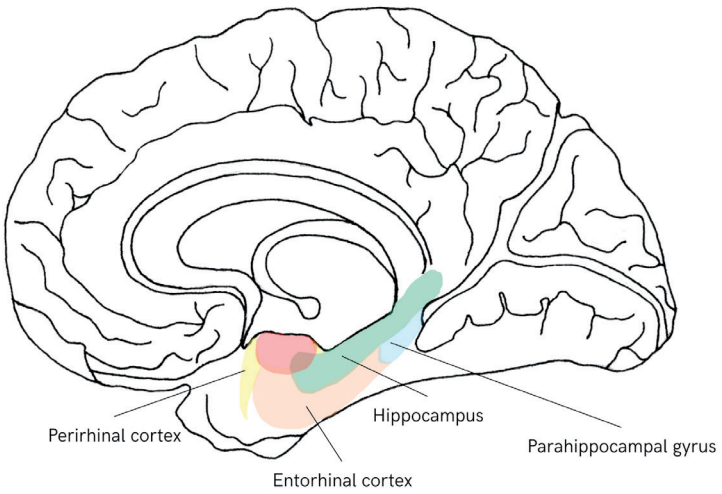

Figure 3. The MTL consists of the hippocampal formation (green) and the parahippocampal gyrus (blue) as well as the entorhinal (orange) and perirhinal (yellow) cortices.

By contrast, the lateral PFC is an effortful system that can be divided into different subregions (Figure 4) and is crucial for organizing information, and for generating and selecting strategic processes (e.g., by generating, maintaining, and selecting semantic associations; Moscovitch, 1992; Fletcher & Henson, 2001; Eichenbaum et al., 2007). Both the MTL and the PFC are matured in younger adults but undergo age-related shrinkage in gray and white matter. Longitudinal and cross-sectional studies have shown that structures in the frontal lobes degenerate earlier, at a steeper rate, and more noticeable than those in the hippocampal region (Raz, 2000; Raz et al., 2005; Lindenberger et al., 2013). Importantly, these age-related differences are accompanied by marked inter-individual variability in brain structure (Raz et al., 2005; Lindenberger et al., 2013; Lindenberger, 2014), and may accordingly contribute to individual differences in associative memory.

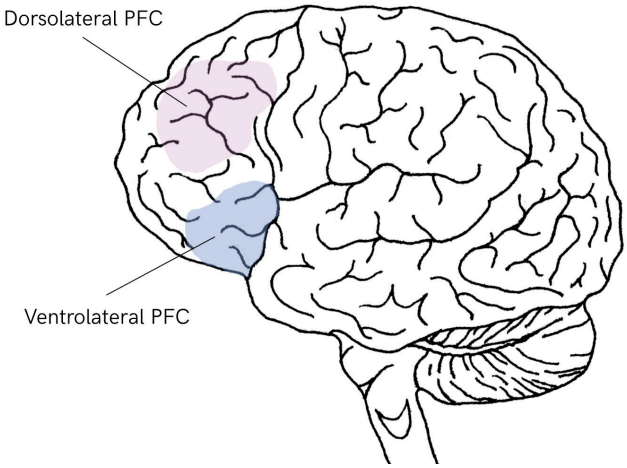

Figure 4. The PFC can be divided into dorsolateral PFC (pink; BA 8, 9, and 46), and ventrolateral PFC (blue; BA 44, 45 and 47).

Other brain factors related to episodic memory are neurotransmitter systems. These include, for example, the dopaminergic system that has been associated with both item and associative-memory functioning in younger and older adults (Cervenka et al., 2008; Lisman et al., 2011). In the following, I will review evidence on the relationships among brain structure, brain function, and the dopaminergic system as related to associative memory.

Structural Brain Factors Underlying Associative Memory

To date, few studies have systematically investigated structural brain underpinnings of individual differences in associative memory in younger and older adults. One way of studying such structural underpinnings is MRI. MRI is a technique that enables measuring tissue characteristics of the brain, such as gray or white-matter volume. Gray matter consists mainly of neuronal cell bodies and their synapses. In contrast, white matter contains long-range myelinated axons, the "arms" of neurons that are bundled to tracts and connect different regions of gray matter in the brain. As cognitive functions (such as associative memory) rely on complex processes across many brain regions, gray matter (as the "operator") and white matter (as the "communicator") are both important for the execution of such functions.

A widely held view is that "bigger is better", i.e., larger gray-matter volume implies less atrophy, which results in more preserved cognitive functions. However, evidence on how associative memory relates to gray-matter volume is mixed (Van Petten, 2004; Van Petten et al., 2004; Raz & Rodrigue, 2006). For example, studies linking gray-matter volume to associative memory in younger adults observed negative or zero correlations between hippocampal volume and associative memory (Van Petten, 2004; DeMaster et al., 2014; Schlichting et al., 2017). Others reported larger hippocampal volume to reliably predict

higher associative-memory proficiency (Rajah et al., 2010a; Poppenk & Moscovitch, 2011). Similarly, studies on the relationship between gray-matter volume and associative memory in older adults provide mixed results. Rodrigue and Raz (2004) examined associative memory using a word-pair recognition paradigm from early to late adulthood, revealing a positive relation between hippocampal volume and associative memory across age. In line with these findings, Shing et al. (2011) examined associative memory in relation to hippocampal subfield volumes in older adults and found a positive relationship of CA3–4 and dentate gyrus subfields to performance. In contrast, one study that investigated age-related differences in associative memory (i.e., spatial and temporal context memory) in relation to hippocampal volume, found a positive relation between gray-matter volume and associative memory in younger, but not older adults, suggesting that older adults might depend less on hippocampal, but likely rely more on frontal regions when forming and retrieving associations (Rajah et al., 2010a).

Strikingly, while the exact contribution of hippocampal volume to associative memory remains unresolved, most studies disregard the potential importance of PFC gray-matter volume in associative memory. The scarce evidence presented here indicates the necessity to further examine the link between local gray-matter volume and associative memory in the context of individual differences.

Functional Brain Factors Underlying Associative Memory

While few attempts have been made to investigate brain-structural underpinnings of associative memory, functional-neuroimaging studies have broadened the understanding of the functional organization of MTL and PFC in associative memory. Functional MRI is a method used to measure neural activity in the brain. Thereby, it uses the BOLD contrast that measures changes in blood flow (i.e., hemodynamic response) associated with energy use in brain cells (Singleton, 2009). This technique relies on the assumption that neural activation in a specific region is coupled with increased blood flow in the same region. Hence, the BOLD contrast serves as an indirect measure of neural activity.

In younger adults, there is a wealth of findings supporting a positive relationship between activity in lateral PFC and MTL and associative memory, indicating that both strategic and associative components contribute to good associative-memory functioning in younger adults. As such, studies have observed greater activity in lateral PFC, especially in regions of the IFG to be related to better associative memory (Achim & Lepage, 2005b; Addis &

McAndrews, 2006; Blumenfeld & Ranganath, 2006; Murray & Ranganath, 2007; Wong et al., 2013). Within the MTL, evidence suggests that greater activity in perirhinal cortex predicts better memory for associations between items and their features (e.g., between an object and its color), while greater activity in hippocampus relates to better memory performance of between-item associations (e.g., between two or more objects; Davachi & Wagner, 2002; Sperling et al., 2003a; Giovanello et al., 2004; Jackson & Schacter, 2004; Mayes et al., 2007; Staresina & Davachi, 2008; Qin et al., 2009; Westerberg et al., 2012). While this functional differentiation has been observed for different stimulus materials and types of associations, little attention has been given to regional brain responses to task-specific factors such as type of instruction (i.e., incidental vs. intentional encoding).

In contrast, few functional MRI studies investigated individual differences in associative memory among older adults. For example, in a sample of older adults activity in PFC was associated with improved source recollection (Duarte et al., 2008). In another study, high functioning (i.e., older adults that showed associative-memory performance similar to younger adults) compared with low-functioning older adults (i.e., those with worse associative-memory performance than younger adults) showed increased fronto-parietal recruitment when correctly rejecting rearranged associations. High-functioning older adults also produced less false alarms and showed superior strategy use compared with low-functioning older adults (Fandakova et al., 2015). These findings suggest that, in aging, individual differences in strategic memory processing and mnemonic control contribute to individual differences in associative memory.

However, most relevant functional MRI studies in older adults examined age-related differences in associative memory by comparing older to younger adults, thereby disregarding individual differences. These studies provided support for PFC contributions to age differences in associative memory. That is, compared with younger adults, older adults showed reduced PFC activity during formation and retrieval of word pairs (Cabeza et al., 1997; Anderson et al., 2000) and face-name associations (Sperling et al., 2003b). Similarly, Rajah et al. (2010b) reported an association between reduced performance in spatial and temporal context retrieval and lower PFC activity in older adults. These data demonstrated an age-related deficit in the ability to suppress task-irrelevant information and monitoring processes. Further, evidence linking age-related reductions in associative memory to lower hippocampal activity comes from studies using word-word (Daselaar et al., 2003), face-scene, and object-location binding (Mitchell et al., 2000).

Taken together, structural and functional MRI studies have shown robust evidence for the involvement of MTL and PFC in associative memory. Importantly, these regions do not only support memory formation and retrieval with local activity but their interaction is also crucial for associative memory.

MTL and PFC Coupling Underlying Associative Memory

Although most studies consider MTL and PFC contributions to memory separately, it is generally agreed that both regions interact in associative-memory formation and retrieval (Simons & Spiers, 2003). Relevant evidence comes from studies investigating functional connectivity, i.e., common co-activations during task performance. The studies presented so far investigated local brain activity during associative-memory tasks. Local brain activity informs about whether or not a certain brain region is active while performing a task, and thus if it is functionally relevant for accomplishing certain cognitive operations. On the other hand, functional connectivity informs about the functional interaction between two or more brain regions, i.e., whether or not certain brain regions are co-active during performance of a task. Functional connectivity can, for example, be measured by correlating individual BOLD time points of two brain regions during associative encoding or retrieval. Such co-activations are thought to reflect brain networks that underlie cognitive functions.

Studies on younger adults suggest strong functional connectivity between the lateral PFC and hippocampus during episodic (Grady et al., 2003), and especially associative memory (Addis & McAndrews, 2006; Gagnepain et al., 2011). For example, activity in hippocampus and IFG was related during encoding of face-name associations (Sperling et al., 2003a). Similarly, activity in IFG has been shown to correlate with hippocampal activity during encoding of associations that individuals later remembered (Long et al., 2010).

Generally, inter-individual differences in functional connectivity increase with age (Lindenberger et al., 2013), and hence could be a factor contributing to individual differences in associative memory in older adults. For instance, Fandakova et al. (2015) reported greater co-activation between the anterior PFC and middle temporal and parahippocampal gyrus in high-performing compared with low-performing older adults. Functional connectivity between these regions was interpreted to reflect control processes underlying the detection of intact word pairs. Similarly, Grady et al. (2003) found differences in the link between frontal and hippocampal activity in older adults that were positively related to individual differences in a recognition task. Taken together, these findings underscore the importance of functional MTL-PFC coupling in associative memory.

While these studies report correlations between brain activity in MTL and PFC during associative memory, coupling between these regions can also be expressed across different brain modalities, i.e., across brain structure and function. Considering structural measures in functional MRI analyses aids the interpretation of local patterns of activity. Specifically, if greater activity in one region relates to smaller brain structure in the same or another region, this activity may be interpreted as compensatory. On the other hand, if the relationship between brain activity and structure is positive, it may indicate that higher brain activity is accompanied by good brain integrity. As such, investigating structure-function associations furthers our understanding of the dynamics of the brain in associative memory (Kalpouzos et al., 2012). However, so far only a few studies have considered the interplay between structural and functional brain characteristics. In younger adults, two studies found a positive relationship between hippocampal volume and activity in PFC during associative encoding (Maillet & Rajah, 2011) and retrieval (Rajah et al., 2011). However, most studies investigating structure-function relationships between MTL and prefrontal regions during memory encoding used a sample of older adults (Rosen et al., 2005; Düzel et al., 2011; Kalpouzos et al., 2012; see Maillet & Rajah, 2013). For example, Daselaar et al. (2015) observed greater activity in regions of the PFC and MTL during associative memory to be related to less white matter in close proximity among older adults. These results suggest that greater activity in older adults might compensate for white-matter decline in nearby regions. Other studies investigated the relation between gray-matter volume and brain activity in older adults. In one study, high-performing in contrast to low-performing older adults exhibited greater activity in lateral PFC during encoding and this activity was related to larger MTL volume (Rosen et al., 2005). Similarly, Maillet and Rajah (2011) found activity in lateral PFC during associative encoding to be positively related to gray-matter volume in the hippocampus. Hence, while most work focuses on how older adults' memory performance can be explained by the structure-function interplay between task-relevant regions, there is still little knowledge on such a structure-function MTL-PFC interplay in younger adults.

Dopaminergic Modulation of Associative Memory

In addition to differences in brain structure and function, individual differences in neurochemistry have been associated with between-person differences in episodic memory (Cervenka et al., 2008; Takahashi et al., 2008; Bäckman et al., 2010; Nyberg et al., 2016). In this thesis, I focus on the dopaminergic system and its role in associative memory.

DA is an organic chemical of the catecholamine family that functions as a neurotransmitter in the brain, i.e., it is a chemical released by neurons to send signals to other neurons. When a presynaptic neuron is firing, DA is released into the synaptic cleft. Here, it binds to DA receptors located in the membrane of the receiving neuron. The receiving neuron then triggers further reactions in the cell. Although the importance of DA in various cognitive functions such as working memory and decision making has long been acknowledged, its role in episodic memory has only recently gained attention (Shohamy & Adcock, 2010; Cools & D'Esposito, 2011; Eppinger et al., 2011). DA is released from the ventral tegmental area to the hippocampus (Gasbarri et al., 1994; Gasbarri et al., 1997). Here, it acts at hippocampal synapses where it is involved in plasticity-related mechanisms like long-term potentiation, i.e., the strengthening of synapses that is thought to underlie episodic memory formation, consolidation, and retrieval (Lisman & Grace, 2005; Shohamy & Adcock, 2010; Lisman et al., 2011). There are various ways of assessing the role of DA in cognition. In pharmacological manipulations, DA receptor activation (i.e., binding to DA) is being in- or decreased and associated changes in cognitive functions are measured (Takahashi et al., 2008; Shohamy & Adcock, 2010). Other approaches include measuring DA receptor density that is thought to reflect DA levels in the brain. Such approaches include the use of PET. PET measures radioactivity of a chemical compound that is injected into a participant's blood stream. The compound binds to a target region in the brain. PET measures binding potential, which reflects the ratio of specific to non-specific binding of the ligand to receptors and is interpreted as an indicator of the density of available DA receptors. Binding potential can then be related to, for example, episodic-memory performance. Another approach is to assess allelic variants of genes that are linked to DA density in the brain and to relate these to behavioral measures like episodic memory (Bäckman et al., 2006; Schott et al., 2006; Li et al., 2010).

In younger adults, there is evidence for the involvement of DA in episodic memory. For example, administration of the amino acid levodopa, a precursor to DA, has been shown to improve memory of newly learned pseudowords (Knecht et al., 2004). Studies using PET reported a positive association between DA receptor binding in hippocampus and verbal (Takahashi et al., 2007) as well as pictorial recall (Takahashi et al., 2008) in healthy young men. Similar effects have been found in studies including older adults. In one PET study, DA receptor density in striatum was positively associated with performance in episodic-memory tasks including item (word and pattern recognition) and associative

memory (paired associate learning; Cervenka et al., 2008). In a more recent PET study, Nyberg et al. (2016) observed a positive relationship between caudate and hippocampal DA receptor density and episodic memory including both item and associative-memory tasks. Moreover, DA receptor density accounted for variation in episodic-memory performance across the adult life span (Bäckman et al., 2000). De Frias et al. (2004) investigated episodic memory in relation to allelic variants of the COMT gene in younger and older adults. This gene produces the DA-metabolizing COMT enzyme. This enzyme is crucial for the metabolic degradation of DA, such that higher metabolism is related to decreases in DA levels. Their findings showed that individuals with the Met/Met genotype, which is associated with lower DA metabolism (i.e., higher DA levels) showed better episodic memory than Val carriers in both age groups. Interestingly, the effect of COMT on episodic memory was found for episodic recall, but not recognition, suggesting some specificity for the role of DA in recollection-based processes. As such, one might assume a specific effect of DA on associative memory, which has been shown to primarily rely on recollection. To conclude, while there is some evidence that DA accounts for individual variation in episodic memory in younger and older adults, its specific role in associative memory remains unresolved.

AIM OF THE THESIS

There is a wealth of evidence that item memory performance is generally higher than associative memory, and that the difference between item- and associative-memory performance is magnified in aging. Yet, the degree of associative-memory functioning varies greatly and the significance of this variability has only recently been acknowledged. The overall aim of this thesis is to further our understanding of what underlies individual differences in associative memory. Potential sources for such individual differences are structural, functional, and neurochemical differences in the brain. Understanding how brain differences are related to associative-memory variation will help revealing which processes underlie successful associative operations (i.e., is it the use of strategies, or rather a binding ability that differs between individuals?). In this thesis we specifically investigated (1) regions in MTL and lateral PFC (structurally and functionally) as well as the DA system and their relation to (2) memory of item-item associations under (3) incidental and intentional encoding instructions to also further our understanding of how learning affects associative memory.

As variability in associative memory is much more pronounced in older than younger adults, one interest of this thesis lied in understanding differences in older individuals. However, we also aimed to provide insights as to whether factors underlying individual differences in younger persons are similar to those in older adults. We therefore investigated a sample of healthy older adults (aged 60 years) and a sample of healthy younger adults (aged 25 years) in two studies each, acknowledging that a direct age comparison remains to be conducted in the future. The specific research questions addressed in these studies are:

In older adults

I. Are there gray-matter volume differences that account for individual differences in associative memory?
II. Do individual differences in associative memory relate to differences in DA genotypes?

In younger adults

III. Do functional brain correlates of associative memory vary depending on how the information is encoded (i.e., incidentally vs. intentionally)?
IV. How are gray-matter volume and brain activity in MTL and PFC coupled during associative encoding?

STUDY SAMPLES

Two study samples were used to address the above-mentioned questions:

Swedish National Study on Aging and Care in Kungsholmen

Study Sample

Older adults' data were collected within a multidisciplinary, longitudinal, population-based study (Swedish National Study on Aging and Care in Kungsholmen or SNAC-K). The general purpose of SNAC-K is to address questions regarding older adults' medical, psychological and social health. In the current project, data from a cohort added in 2010 to 2013 were used (wave 4 in SNAC-K). The 678 participants in this cohort were 60 years old and randomly selected from population registries. Within this sample, a subsample of 57 individuals, who passed the screening (e.g., no neurological disorder, no metal operated in their body), participated in an additional MRI session (SNAC-K 60 MRI subsample). The examination in SNAC-K took about 6 hours and consisted of three parts: a nurse interview, a medical examination, and a neuropsychological testing session. In addition to the standard cognitive test battery of SNAC-K (Laukka et al., 2013), this cohort underwent an item-associative memory task that was central in this thesis.

Item-Associative Memory Task

During encoding, participants were presented with 24 face-scene picture pairs on a computer screen and instructed to memorize both the single pictures and their combinations. This was followed by a distractor task, in which subjects had to count backwards from 89 in steps of two for one minute. This task was included to eliminate the influence of short-term memory. Immediately after the distractor task, three self-paced recognition tasks were administered. In the item-memory tasks, subjects saw 16 single pictures (i.e., 16 faces or 16 scenes) of which half had been studied during encoding and the other half served as novel lures. In the associative-memory task, subjects saw 16 face-scene pairs. All pairs had been studied during encoding, but half of the pairs were intact (old) and the other half was recombined (composed of faces and scenes that appeared in the encoding phase, but not together). Participants were told to indicate whether they had studied a particular item or item pair by pressing the buttons "yes" or "no" on a computer keyboard (Figure 5).

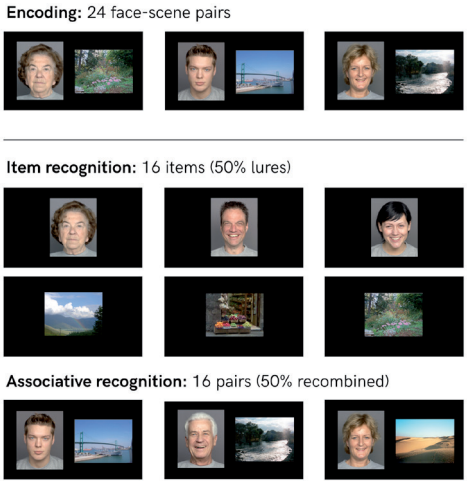

Figure 5. Experimental design and exemplar trials from the item-associative memory task. During encoding, participants were presented with face-scene picture pairs and instructed to memorize both the single pictures and their combinations. At retrieval, three self-paced recognition tasks were administered, two item-memory tasks, and one associative-memory task.

MRI Assessment

Scanning was performed at the MR Research Center, Karolinska Institutet, Solna, Sweden, with a 3T GE750 scanner and a 32-channel head coil. To assess gray-matter volumes, T1-weighted MRI scans were collected using the SAG FSPGR BRAVO sequence. Exact details regarding the pulse sequence parameters are described in the Methods section of study I.

Genetic Assessment

DNA was extracted from peripheral blood samples using standard methods. The SNPs were genotyped using MALDI-TOF analysis on the Sequenom MassARRAY platform at the Mutation Analysis Facility, Karolinska Institutet (Darki et al., 2012). Quality control was performed at DNA sample level, assay level, and the level of multiplex assay pool. DA receptor-related genetic variations assessed included the DRD1 polymorphism (rs4532; T/T, C/T, C/C), DRD2 (ANKK1/TaqIA; rs1800497; A2/A2, A2/A1, A1/A1) and DRD3 (Ser9Gly; rs6280; T/T, T/C, C/C). Genetic variations associated with Alzheimer's disease included APOE (rs429358; e2/e2, e2/e3, e2/e4, e3/e3, e3/e4, e4/e4), PICALM (rs3851179; rs541458; C/C, T/C, T/T), BIN1 (rs744373; G/A, G/G), and CLU (rs11136000; C/C, T/C, T/T).

Kungsholmen Young

Study Sample

The Kungsholmen Young sample included data from 96 younger adults (mean age of 25 years) collected during 2014. Younger individuals underwent an adapted examination including a subset of cognitive and non-cognitive variables and the same MRI assessment as the SNAC-K 60 MRI subsample. Additionally, a subsample of 57 participants performed an in-scanner functional MRI task (Kungsholmen Young fMRI sample).

In-Scanner Item-Associative Memory Task

During encoding, which was performed in the scanner, participants were presented with 180 trials containing pictures of common objects combined as object pairs or object triplets (associative encoding) and 180 trials containing pictures of single objects fragmented in two or three pieces (item encoding). Object fragmentation was done to (a) keep the visual input comparable between associative and item trials, and (b) induce a low-level perceptual binding process in the item condition to ensure that potential differences between associative and item encoding related to differences in higher-level binding processes and not to differences in the binding of perceptual inputs (Figure 6). Participants were split into two groups that received different encoding instructions. The intentional-encoding group was instructed to memorize single objects and object combinations for a subsequent recognition task. The incidental encoding group was not informed about a subsequent recognition task, but told a cover story that the task was of perceptual nature and that they should perform animacy judgments on the objects presented. Immediately after scanning, participants were brought into a separate room to perform a recognition task that tested memory of the objects and object combinations presented during encoding. Associative recognition included 63 old trials, 18 new trials, and 27 rearranged trials (composed of object images that appeared in the encoding phase, but not together). Item blocks contained 90 old trials and 18 new trials. Old trials consisted of one intact object presented in fragments during encoding. New trials consisted of an intact but new object that was not shown during encoding. Participants were instructed to indicate with a button press whether they had seen the object or object combination during encoding.

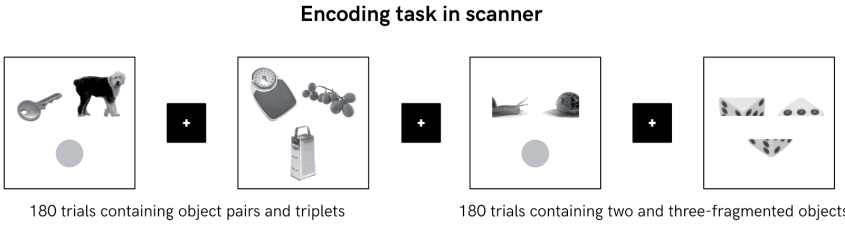

Figure 6. Exemplar trials from the in-scanner item-associative memory task. During encoding, participants were presented with four types of experimental trials (i.e., object pairs, object triplets, two-fragmented items, and three-fragmented items).

MRI Assessment

Scanning was performed at the MR Research Center, Karolinska Institutet, Solna, Sweden, with a 3T GE750 scanner and a 32-channel head coil. In line with the protocol used in SNAC-K, T1-weighted MRI scans were collected using the SAG FSPGR BRAVO sequence to assess gray-matter volume. Functional MR data were collected using a gradient echo pulse sequence. Exact details regarding the pulse sequence parameters are described in the Methods sections of studies III and IV.

BRAIN IMAGING ANALYSIS

Structural MRI Preprocessing and Analysis

To analyze gray-matter volume in relation to associative-memory performance, we used an automated analysis technique called VBM. VBM allows for gray-matter volume comparisons at each voxel across individual brains. A voxel is the unit that a 3D MR image is built of. It is an image building block analogous to the 2D pixel of computers screens or digital cameras. Each voxel represents a small cube of brain tissue with a million or so brain cells. VBM statistically compares brain voxels across individuals; thus, even small differences in gray-matter volume can be observed. The VBM analysis was performed in Statistical Parametric Mapping 12b (Functional Imaging Laboratory, Wellcome Department of Imaging Science) implemented in MATLAB R2012b (The MathWorks Inc., Natick, MA). First, the individual T1-weighted images were segmented into gray matter, white matter, and cerebrospinal fluid. To successfully perform analyses across different individuals (i.e., group analyses), the same anatomical location needs to be sampled for each person. However, people differ largely with regard to their brain anatomy, hence the images of all participants need to be registered to a common template. Therefore, a sample specific template was created using DARTEL with customized templates, an algorithm for diffeomorphic image registration (Ashburner, 2007). This template is created based on participants' brain structure. As such, the template obtained via DARTEL is an optimized one that is the most representative of the sample. DARTEL creates a series of 7 templates; Template-0 (the first template created) is simply an average of all individual brains. The aim of DARTEL is to optimize this template, i.e., it allows a more precise inter-subject alignment. At each iterative step, the deformations for each voxel of each brain (the deformations applied to match the template at each step) are encoded in a single subject-specific flow-field. DARTEL uses millions of parameters (three for each voxel) to model the shape of each brain. In turn, based on the updated flow fields, a new crisper template is created, and so forth, until Template-6. In other words, DARTEL generates its own increasingly crisp average template, to which the images are iteratively aligned. For reporting of the results in known common space, an additional registration to the MNI template (widely used in neuroimaging research) was performed. Finally, the data were smoothed by averaging data over adjacent voxels with a Gaussian kernel, so that each voxel represented the average of itself and its neighbors. In all studies of this thesis, we applied a kernel of 8 mm FWHM. The advantage of data smoothing is that it removes noise, and hence improves the signal-to-noise ratio. It further makes parametric errors more normally distributed and

therefore improves the validity of the statistical tests performed on the data.

VBM analysis can be used to answer questions such as "How do differences in gray-matter volume in voxels across the brain account for differences in associative-memory performance between individuals?". Such questions can be addressed with multiple regressions within the framework of the GLM. That is, at each voxel, variability in gray-matter volume is modeled as a linear combination of, for example, an experimental outcome (e.g., memory performance), confounding effects of no interest (e.g., intracranial volume, age or sex) and residual variability. As such, correlations between a task variable (e.g., memory performance) and gray-matter volume can be examined.

Functional MRI Preprocessing

The functional MRI data for this thesis were preprocessed and analyzed using Statistical Parametric Mapping 12 (Functional Imaging Laboratory, Wellcome Department of Imaging Science) implemented in MATLAB R2014b (The MathWorks Inc., Natick, MA). Before analyzing the data statistically, we applied a commonly used preprocessing pipeline that included a number of computational steps to reduce artifacts and noise-related components inherent in the data. First, we applied slice-time correction of the functional MRI data. MR images are acquired in a series of successively measured 2D slices, which causes a slight temporal displacement between subsequent slices. For example, for a functional MR image of 46 slices taken in 3 seconds, the last slice is measured almost 3 seconds after the first slice. Slice-time correction changes the data in a way as if the whole volume would have been measured at exactly the same time. Further, we corrected the data for head movements that seriously hamper the quality of MRI data. In so doing, we aligned all image volumes to the first image volume of the respective experimental run. The functional MRI data were further co-registered to each individual's structural T1-image and spatially normalized to the group-specific DARTEL template. To transform all data into common space, we spatially normalized each individual's data to the standard MNI template. Finally, the data were smoothed with a Gaussian kernel of 8 mm FWHM.

Functional MRI Analysis

The primary interest in functional MRI analyses is to examine how brain activity is linked to a specific psychological process such as memory encoding. This could mean asking the question "Which areas in the brain are more active when a person is intentionally encoding associative information compared to when incidentally encoding the same information?". Although expe-

rimental tasks are designed to be identical except for differing with regard to the experimental manipulation (e.g., the encoding instruction), the brain is still likely to show differences in brain activity due to noise from the imaging process or other factors unrelated to the task. Therefore, statistics are used to identify the most significant differences above and beyond background brain activity or noise.

In study III, we analyzed the functional MRI data by modeling the BOLD signal time series from each voxel in the brain as a separate dependent variable and the effects of the experimental manipulation with multiple regression using the GLM framework. First, the model needs to be specified, which is done on the individual subject level. Here, conditions (comprising the experimental manipulations) are defined as a set of regressors thought to account for differences in brain activity. The regressors are then convolved with a hemodynamic response function. Additionally, nuisance regressors can be added to the model that include realignment parameters derived from the head motion-correction procedure during preprocessing. Once the model is specified, parameter weights (βs) of each regressor can be estimated. Contrast images can then be generated that entail, for each voxel, the estimated difference in parameter weights between experimental conditions (e.g., contrasting activity in each voxel during intentional and incidental associative encoding). Importantly, functional MRI does not assess absolute values of brain activity; statistical analyses always involve contrasting two conditions. The resulting subject-level contrast images can then be used for hypothesis testing on the group level. Results are presented in statistical parametric maps that contain a t-statistic for each voxel in the brain, thresholded at a specific alpha level to determine which voxels show statistically significant activity in one relative to another experimental condition.

Multimodal Analysis

Instead of examining structural T1-weighted as well as functional MRI data separately using statistical parametric mapping, different data modalities can be analyzed jointly to study interactions between, for example, structural and functional MRI data (using for example ICA). ICA is a method that separates a set of mixed signals into its individual source signals. The underlying assumption behind ICA is that source signals are based on independent physical processes and therefore statistically independent from each other. The principle of ICA is commonly illustrated with the help of a cocktail party problem: Several people are talking simultaneously and a few microphones record the speech signals. The recording of each microphone is an ex-

ample of a mixture of the independent voices. The cocktail party problem also applies to fMRI data. At each data point, the recorded signal can be considered as a neuronal mixture of underlying independent components. The objective of ICA is to find a matrix that allows the recovery of the original source signals. The signals are separated, so that statistical independence is maximized. JICA as applied to different modalities extracts maximally spatially independent sources that are coupled together by a shared loading parameter. JICA first requires the selection of brain features that may include, for example, a gray-matter volume image and a functional MRI contrast image for each participant. As different features have different ranges, their units need to be normalized. Hence, the features are sampled to have the same voxel size and the same average sum-of-squares across all subjects and all voxels for each modality. After normalization, a feature matrix is composed that places the features side by side. This feature matrix is further decomposed into spatially maximally independent component images and subject-specific loading parameters. The resulting loading parameters can then be statistically compared between different experimental groups or correlated with cognitive measures such as associative memory performance.

SUMMARY OF STUDIES

STUDY I. STRUCTURAL BRAIN CORRELATES OF ASSOCIATIVE MEMORY IN OLDER ADULTS

Background

In this study, we investigated the relationship between regional gray-matter volume and associative memory in a sample of healthy older adults. To date, only a few structural MRI studies have systematically investigated this relationship. Moreover, most studies focused on regions in the MTL and have not controlled for item memory (Rajah et al., 2010a; Shing et al., 2011). While hippocampal gray-matter volume differences could be one source for differences in associative memory, such differences might also stem from strategic processes linked to PFC. Specifically, for memory tasks that require intentional encoding and retrieval of item-item associations, participants need to rely on monitoring and strategic processes. Hence, in this study we expected individual differences in associative memory to be at least partly accounted for by volumetric differences in PFC.

Methods

The sample included 54 older participants from the SNAC-K 60 MRI subsample (30 females; 60 years old), who underwent the item-associative memory task and MRI assessment, in which T1-weighted images were collected.

To investigate item and associative-memory performance, we determined hits, false alarms and hits-false alarms separately for all three recognition tests of the item-associative memory task described previously containing face-scene pictures pairs. To control for a potential confound of task difficulty between item and associative memory, a second free recall item-memory task was included. Here, participants studied 16 concrete Swedish nouns, presented in black on white paper. Each word was shown and read out aloud by the experimenter. Immediately after presentation of the last word in the series, participants were given 2 minutes to recall the words orally (Laukka et al., 2013). Gray-matter volume was analyzed using VBM. We performed multiple regressions, regressing gray-matter volume on associative memory while controlling for item recognition and free recall. Regions of interest in which the analyses were performed included bilateral dorsolateral and ventrolateral PFC as well as the hippocampal and parahippocampal gyri.

Results

Behaviorally, participants performed significantly worse in the associative-memory task compared with the two item-memory tasks. This effect stemmed mainly from higher false-alarm rates

in associative compared with item memory, whereas hit rates did not differ across tasks. Importantly, associative memory was independent of individuals' ability to remember single items. Better associative-memory performance (i.e., higher hits-false alarms rate) was related to larger gray-matter volume in left dorsolateral PFC (Figure 7). Analysis of hit rates revealed a positive relation to gray-matter volume in right dorsolateral and ventrolateral PFC. Finally, participants with fewer false alarms had larger gray-matter volume in right ventrolateral PFC.

Conclusion

Our findings provide evidence for the importance of the PFC in intentional learning of item-item associations. The dorsolateral and ventrolateral PFC have previously been related to information maintenance, binding, inhibition, monitoring, and control processes during encoding and retrieval of item pairs as well as the self-initiated use of memory strategies (Fletcher et al., 2000; Wagner et al., 2001; Wheeler & Buckner, 2003; Bunge et al., 2004; Kirchhoff et al., 2014). This suggests that organizational and strategic processes distinguish older adults with good from those with poor associative memory.

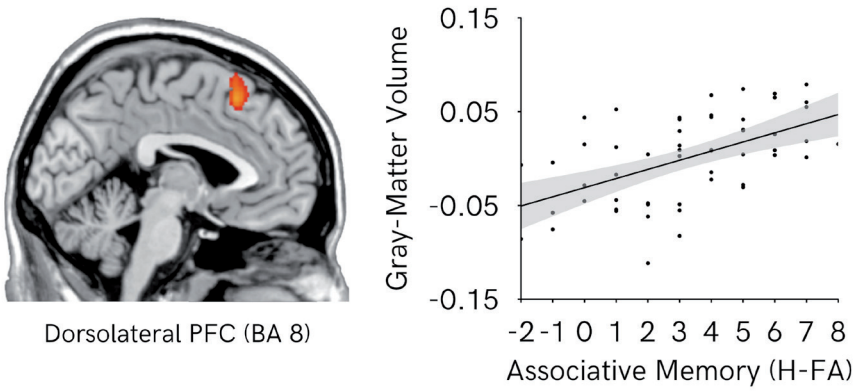

Figure 7. Gray-matter volume correlates of associative memory in a sample of older adults. Left dorsolateral PFC (BA 8) was positively related to hits-false alarms (H-FA) in associative memory. Each dot represents one participant. Shaded area represents the 95% confidence interval.

STUDY II. DOPAMINE RECEPTOR GENES MODULATE ASSOCIATIVE MEMORY IN OLD AGE

Background

Previous studies have observed substantial inter-individual differences in associative memory in older adults (Nyberg et al., 2003; Brehmer et al., 2007). Further, it has been suggested that differences in neurochemistry such as dopaminergic modulation could be one potential factor underlying variability between individuals in episodic memory (Bäckman et al., 2010). In this study, we investigated the influence of DA receptor genes on item

and associative memory and hypothesized that differences in dopaminergic neuromodulation would affect associative memory more than item memory, because of work that has shown a differential effect of DA on familiarity and recollection (de Frias et al., 2004). This is based on research indicating that recollection is vital to associative memory, whereas item memory may also draw on familiarity (Yonelinas, 1997; Diana et al., 2008).

Methods

The sample included 525 older participants from the SNAC-K sample that underwent the item-associative memory task as well as genetic assessment (302 females; age = 60 years). We examined the effects of three DA-relevant SNPs: D1 (DRD1; rs4532), D2 (DRD2/ANKK1/Taq1A; rs1800497), and D3 (DRD3/Ser9Gly; rs6280) receptor genes that capture individual differences in DA receptor density. These genotypes were combined into a single genetic score (Papenberg et al., 2013; Ferencz et al., 2014). That is, for each of the SNPs, we identified a disadvantageous genotype for memory. Genotypes were defined as disadvantageous if they had been associated with lower receptor density or cognitive performance (i.e., the DRD1 T allele, the DRD2 A1 allele, and the DRD3 C allele were considered disadvantageous). Individuals with two disadvantageous alleles were assigned a value of 3, whereas carriers of one or no disadvantageous alleles were assigned values of 2 and 1, respectively. Participants were then split into two groups: low-risk (values 3 to 6) and high-risk (values 7 to 9) profiles, and the effect on hits-false alarms for item and associative memory were determined. In addition, we investigated whether genes related to risk for Alzheimer's disease: APOE (rs429358), PICALM (rs3851179 and rs541458), BIN1 (rs744373), and CLU (rs111360000) would show similar effects as DA receptor genes on item and associative memory.

Results

Individuals with less beneficial DA genotypes (high-risk profile group) performed worse in the associative-memory task compared with carriers of more beneficial genotypes (low-risk profile group). However, no such group differences were found with regard to item memory (Figure 8). Importantly, individuals with less beneficial compared with more beneficial genotypes that were associated with Alzheimer's disease performed worse in both the item- and the associative-memory task.

Conclusion

Our results suggest that DA may be particularly important for associative memory, probably because of a stronger contribution

of receptor density to associative compared to item memory. In contrast, genetic variations associated with Alzheimer's disease may influence episodic memory overall in older adults without dementia.

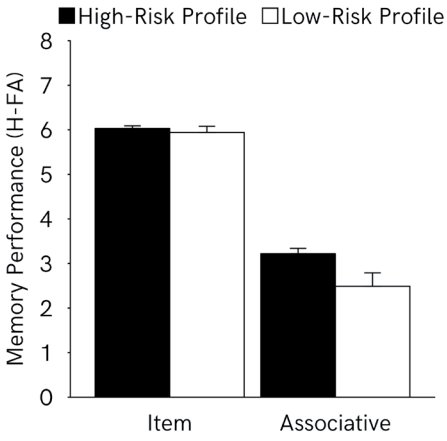

Figure 8. Item and associative memory performance for carriers with less beneficial DA genotypes (high-risk profile group; black) and more beneficial DA genotypes (low-risk profile group; white). While the groups did not differ in item memory, the high-risk profile group performed significantly worse than the low-risk profile group in the associative-memory task. Error bars represent standard errors around the means.

STUDY III. DIFFERENTIAL EFFECTS OF ENCODING INSTRUCTIONS ON NEURAL CORRELATES OF ITEM AND ASSOCIATIVE MEMORY

Background

Generally, individuals perform better in item- than in associative-memory tasks (Naveh-Benjamin, 2000; Kamp & Zimmer, 2015), possibly because associative memory requires additional cognitive operations to generate relations between items (i.e., binding and strategic processes; Addis & McAndrews, 2006). On this view, item-memory formation does not require intentional learning instructions, but may occur as a by-product of perceptual processing (levels of processing model; Craik & Lockhart, 1972; Craik & Tulving, 1975). Similarly, brain activity in MTL regions and IFG during intentional item encoding has been shown to resemble encoding activity during incidental item encoding (Buckner et al., 2001; Stark & Okado, 2003; see Henson, 2005). However, the modulatory effect of instructions on associative memory remains uncertain, as most studies have investigated associative encoding under either intentional or incidental-encoding instructions without a direct comparison (Jackson & Schacter, 2004; Chua et al., 2007; Qin et al., 2007; Park & Rugg, 2011). Therefore, in study III we investigated similarities and differences in functional brain correlates of item and associative memory as a function of encoding instruction. We hypothesized a stronger modulatory effect of type of instruction for associative than for item memory. Specifically, we expected differences in brain activity in MTL and IFG to be

greater between intentional and incidental associative encoding compared with instruction-related differences for item encoding.

Methods

This study included 51 younger participants (27 females; M_{age} = 25 years) from the Kungsholmen Young fMRI sample who underwent the in-scanner item-associative memory task previously described. Twenty-seven participants received intentional and 24 participants were given incidental encoding instructions. After completion of the item-associative memory task, individuals were asked if and what kind of memory strategy they were applying during encoding to remember the objects and object combinations. To examine performance differences between groups, we compared hits-false alarms of the item and associative recognition tasks. With regard to our main research question, we identified brain areas in which intentional encoding differed from incidental encoding of associations and items. Further, we determined regions that showed greater activation during encoding of associations relative to items. Finally, we conducted a functional-connectivity analysis to investigate which brain areas interacted with the hippocampus during successful intentional encoding.

Results

Subjects remembered more items than associations in the recognition task, independently of encoding instruction. Moreover, all participants who received intentional encoding instructions reported the use of memory strategies during encoding (e.g., sentence generation, visual imagery). On the neural level, we observed significantly greater activity in left anterior hippocampus during intentionally compared with incidentally encoded associations, while activity in this region did not differ between intentionally and incidentally encoded items (Figure 9). Further, greater activity in left anterior hippocampus and left IFG was observed during intentional associative compared to intentional item encoding. Follow-up analyses revealed that the magnitude of anterior hippocampal and IFG activity was related to subsequent memory of intentionally encoded associations. Similarly, connectivity of the anterior hippocampus to the right superior temporal lobe and IFG related to subsequent memory of intentionally encoded associations.

Conclusion

Study III provided further evidence that the hippocampus and left IFG are involved in successful encoding of associative information as well as in processes related to attempts to

remember associative information. They moreover supported previous observations on the importance of the functional linkage of MTL-IFG regions in associative-memory formation (Addis & McAndrews, 2006; Gagnepain et al., 2011). Finally, our findings demonstrated differential involvement of the left anterior hippocampus in intentional relative to incidental encoding of associations. This suggests that the intent to remember triggers a binding process accomplished by this region. Moreover, the underlying processes of associative binding as indicated by differential hippocampal recruitment suggest qualitative differences between incidental and intentional associative encoding in younger adults.

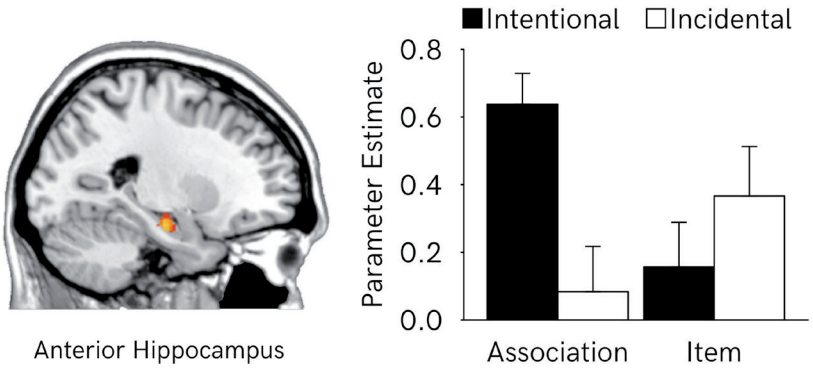

Figure 9. Activity in the left anterior hippocampus was greater during intentionally compared with incidentally encoded associations, while activity in this region did not differ between intentionally and incidentally encoded items. Mean participant-specific β-weights of voxels within this region are plotted separately for encoding groups and experimental conditions. Error bars represent standard errors of the means.

STUDY IV. STRUCTURE-FUNCTION ASSOCIATIONS OF SUCCESSFUL ASSOCIATIVE ENCODING

Background

Functional MRI studies have established the importance of brain activity in the hippocampus and IFG during associative encoding (Jackson & Schacter, 2004; Prince et al., 2005; Staresina & Davachi, 2006). Similarly, evidence from structural MRI studies suggests a relationship between gray-matter volume in these regions and associative memory (Van Petten, 2004; Rajah et al., 2010a; Poppenk & Moscovitch, 2011). From functional-connectivity studies, we know that the hippocampus and IFG are strongly coupled during successful associative encoding (Sperling et al., 2003a; Addis & McAndrews, 2006; Gagnepain et al., 2011). In this study, we aimed to extend past findings on functional connectivity to structural-functional connectivity in a sample of younger adults. Specifically, we examined how gray-matter volume is associated with brain activation during successful associative-memory formation in regions of the MTL and IFG.

Methods

Data from 24 participants of the Kungsholmen Young fMRI sample were used (14 females; M_{age} = 25 years). All participants received intentional learning instructions in the in-scanner item-associative memory task while scanned with MRI. Additionally, they underwent structural MRI in which T1-weighted images were obtained. We conducted two types of analysis: First, we applied VBM to identify gray-matter volume correlates of associative memory in the hippocampus and IFG. Second, using jICA, we investigated whether functional activation patterns within the MTL-IFG circuit could be locally or distally accounted for by gray-matter volume.

Results

Unimodal analyses using VBM revealed that participants with better associative memory showed larger gray-matter volume in left anterior hippocampus. Further, the jICA revealed one independent component that comprised a covariance pattern between gray-matter volume in anterior and posterior MTL and encoding-related activity in IFG. Importantly, individual component loadings were positively linked to hits-false alarms in associative memory, suggesting that individuals with stronger structure-function coupling encoded the associations more proficiently (Figure 10).

Conclusion

Our findings suggest that hippocampal gray matter modulates distally distinct parts of the associative encoding network, thereby extending previous demonstrations of MTL-IFG functional connectivity during associative memory formation in younger adults.

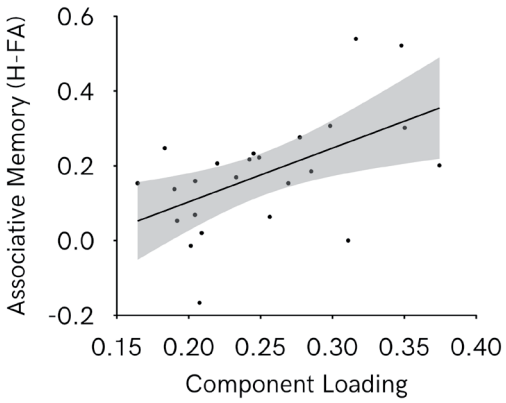

Figure 10. Individual component loadings were related to associative-memory performance (H-FA; r = .54, p = .007). Each dot represents one participant. Shaded area represents the 95% confidence interval.

DISCUSSION

The aim of this thesis was to scrutinize potential underlying neural sources of individual differences in associative memory. In three studies we investigated gray-matter volume and brain activity contributions of the MTL and lateral PFC to associative memory (studies I, III, and IV). Furthermore, we addressed whether associative memory and its associated brain activity are affected by learning instructions (incidental vs. intentional; study III). We also examined the specific contribution of the dopaminergic system to associative memory, as measured using DA receptor genes (study II).

In the following, I will first discuss the structural and functional brain findings separately for PFC, MTL, and their interplay, before discussing the results regarding the DA system. I will then address some of the limitations and future directions of this work, followed by concluding remarks. As we have investigated samples of healthy older and younger adults in two studies each, the findings will be discussed across both age groups, including ideas as to how the results might have looked like in the age group that was not investigated in the respective study.

Differential Contributions of MTL and PFC to Associative Memory in Younger and Older Adults

To date, evidence for brain volume-cognition relationships in healthy adults is mixed and varies as a function of type of cognitive measure, age of the study sample, and regions of interest that have been investigated (Van Petten, 2004; Poppenk & Moscovitch, 2011; Kirchhoff et al., 2014). With regard to associative memory, most studies in younger and older adults investigated gray-matter volume correlates of memory performance in MTL (e.g., Rajah et al., 2010a; Poppenk & Moscovitch, 2011; Shing et al., 2011; Schlichting et al., 2017), while disregarding potential effects in PFC. In study I and study IV, we sought to overcome this bias by investigating gray-matter volume contributions of both the MTL and lateral PFC to associative memory. Interestingly, in older adults individual differences in associative memory related to gray-matter volume in left and right dorsolateral and ventrolateral PFC (BAs 8, 45, 46, and 47; study I), whereas in younger adults differences in associative memory performance related to gray-matter volume in the left anterior hippocampus (study IV).

In this thesis, we provide no direct comparison between younger and older adults. Still, the associative memory tasks participants performed in study I and IV were very similar, and therefore might allow for some comparison between age groups. Specifically, in both tasks subjects were required to encode picture pairs intentionally, followed by an associative-recognition task. The only task-related differences between the two studies

concerned the stimulus material and the number of trials. As such, one would assume that the approach with which participants could have successfully solved associative encoding and recognition should be fairly similar across studies I and IV. However, the differential contributions of regional gray-matter volume suggest that the mechanisms underlying individual differences in associative memory might have differed between younger and older adults – as opposed to being related to differences between the actual memory tasks. According to the two-component framework described previously (Shing et al., 2008) and the roles attributed to PFC and MTL in episodic memory, our findings suggest that individual differences in associative memory in older adults largely reflected differences in the strategic component, while variability in associative memory in younger adults primarily seemed to reflect the binding component. Further evidence thereof comes from study III. Here, almost all participants in the intentional encoding group reported having used a deep encoding strategy to remember the item-item associations. This suggests that, under intentional encoding instructions, younger adults' associative-memory performance differed mostly with regard to binding processes drawing on the hippocampus.

The notion of a relatively greater contribution of the strategic than the binding component to associative memory in older adults raises the question of what characterizes these strategic operations. Some suggestions pertaining to this issue are discussed next.

Processes Associated With PFC Volume

In study I, we observed large heterogeneity in associative-memory performance between older individuals that was related to volumetric differences in dorsolateral and ventrolateral PFC. Generally, PFC regions have been found to support hippocampal binding with a variety of attentional and organizational mechanisms (Addis & McAndrews, 2006; Murray & Ranganath, 2007; Qin et al., 2009). We found our effects to be located in bilateral dorsolateral (BAs 8 and 46) and ventrolateral (BAs 45, 47) PFC. These areas are relatively large and contain multiple subregions that serve distinct functions (Henson et al., 1999; Blumenfeld & Ranganath, 2006; Blumenfeld et al., 2011). For example, Blumenfeld et al. (2011) showed that ventrolateral PFC is involved in maintaining and retrieving goal-relevant item information, while ventrolateral and dorsolateral PFC are both recruited during processing of item-item associations. In another study, Kirchhoff and Buckner (2006) demonstrated that activity in ventrolateral PFC (BAs 45 and 47) was positively related to use of a verbal elaboration strategy during associative encoding. Yet

another study showed dorsolateral PFC (including BAs 46 and 8) to be involved in episodic retrieval monitoring (Achim & Lepage, 2005a). Hence, between-person differences in associative-memory performance could be based on multiple factors (Devitt & Schacter, 2016). In addition to involving relatively large brain areas, there is a crucial disadvantage inherent to structural MRI studies: Methodologically, it remains impossible to disentangle if variation in gray-matter volume is related to variation in encoding or retrieval processes. That is, even if we could reduce potential strategic or control processes to smaller brain areas, we could not make any claims about whether brain-related factors that differed between individuals were linked to encoding or retrieval. For example, if attention is disrupted at encoding by increased distractibility or if visual exploration does not take place, associations might not even enter the encoding process (Healey et al., 2008). At retrieval, the general observation that older adults increasingly rely on familiarity might lead to increased difficulty to distinguish between overlapping information, which could make some older adults especially vulnerable to false alarms (Jacoby & Rhodes, 2006). This effect seems to be particularly likely to occur when items have pre-existing semantic representations like in our study, in which we used concrete items (i.e., faces and scenes; Koutstaal et al., 2003; Pidgeon & Morcom, 2014). To conclude, given our findings of associative memory relating to gray-matter volume in several PFC subregions, a variety of strategic and control processes could account for the observed individual differences in memory performance among older adults.

It is reasonable to assume that the processes discussed above contribute to associative memory in older adults, yet binding two or more items is of course a prerequisite for associative memory formation and retrieval. Hence, our findings do not preclude the involvement of MTL in associative memory in aging. However, we only observed volumetric differences in MTL regions as related to associative memory in younger adults, which calls into question why that is.

MTL Contributions to Associative Memory

Because binding is a prerequisite for remembering item-item associations, the lack of hippocampal gray-matter volume contribution to associative memory in older adults might appear surprising. At the same time, in reviewing the literature, the relationship between hippocampal volume and memory performance is not universally observed (Kaup et al., 2011). For example, Gorbach et al. (2017) recently conducted a longitudinal study and reported a significant association between episodic

memory decline and hippocampal atrophy for older adults ranging between 65 and 80 years, but not for persons in the age range between 55 and 60 years (cf. the current older sample). Here, the findings were interpreted such that decline of brain markers and cognitive measures becomes more pronounced after the age of 65 years, which is why associations may not be detected at earlier ages. In line with this, the previously mentioned findings from Shing et al. (2011) of a positive relationship between smaller hippocampal volume and higher false alarm rates were based on an old-old adult sample. Together, these findings may suggest the importance of maintaining MTL volume for associative memory functioning in aging, but they also may indicate the crucial importance of hippocampal volume after the age of 60 years. However, the fact that we did find hippocampal volume explaining variance in associative memory in adults aged 20 to 30 years contradicts the aforementioned notion that solely the decline of brain markers and cognitive measures enables the observation of volume-cognition relationships. Still, as the SNAC-K 60 cohort returns for follow-up 6 years after the baseline assessment, it would be very interesting to examine whether a contribution of hippocampal gray-matter volume to associative memory becomes apparent at follow-up.

In addition to investigating brain volume correlates of associative memory in MTL and PFC, we studied the coupling between these two regions and how this would relate to individual differences in associative memory. This issue was addressed in study IV using the younger-adult sample.

The Importance of MTL and PFC Coupling for Associative Memory

Having investigated hippocampal and prefrontal gray-matter volume contributions to associative memory independently, we also examined the structural-functional interplay of these regions during associative encoding in younger adults (study IV). To date, few studies have investigated distal structure-function relationships in younger adults, as they pertain to associative memory. Therefore, in study IV we aimed to fill a knowledge gap on how the associative brain network operates to successfully accomplish encoding and retrieval, and how network properties differ between individuals. In study IV, we observed a covariance pattern between gray-matter volume in anterior and posterior MTL (i.e., volume in hippocampus and parahippocampus) and encoding-related activity in IFG. Importantly, individuals with greater expression of this structure-function relationship showed better associative-memory performance. Thus, variability in the strength of MTL-IFG coupling contributed to individual

differences in associative memory in younger adults. To date, most studies on MTL-IFG coupling were modality specific and investigated functional connectivity in relation to associative memory. These studies have observed functional connectivity between hippocampus and IFG during associative-memory formation (Sperling et al., 2003a; Addis & McAndrews, 2006; Gagnepain et al., 2011). The findings from study IV extend these findings demonstrating that structural-functional coupling between MTL and IFG promotes successful associative encoding in adulthood. Interestingly, the regions in IFG (i.e., BAs 45 and 47) found to be coupled with anterior and posterior MTL volume were overlapping with regions relevant to associative memory in older adults (study I). In contrast to study I though, here we know that activity in these regions relates to processes at associative encoding as we used functional MRI. As discussed previously, activity in BAs 45 and 47 during associative encoding might have reflected deep encoding processes, such as the use of verbal elaboration (Kirchhoff & Buckner, 2006). Our findings suggest that these processes are coupled with volumetric features of the anterior and posterior MTL that may serve in binding item-item associations (Sperling et al., 2003a; Backus et al., 2016). Interestingly, neither activity in IFG nor MTL regions related to gray-matter volume in the same respective region. This suggests that gray-matter volume and function are not linked in an obvious fashion (i.e., larger volume, greater activity). Rather, their interaction is complex and stretches across different distal brain regions.

Having observed this structure-function relationship of anterior and posterior MTL to IFG in younger adults, it would be interesting to examine if a similar relationship in older adults would be seen. This would help to better understand the trajectory of individual differences in associative memory across the life span. More precisely, if proficient associative memory reflects maintaining structural and functional integrity during aging, then this should result in a positive relationship between MTL structure and PFC function across time. Older adults with larger MTL gray-matter volume would recruit PFC to a greater extent, which again would relate to better associative-memory performance. Alternatively, older individuals with proficient compared to poor associative memory might overactivate PFC regions to compensate for structural MTL losses. This would result in a negative relationship between these measures and a positive relationship between MTL-PFC coupling and associative memory performance. Some studies have already addressed structure-function relationships in older adults (Braskie et al., 2009; Maillet & Rajah, 2011, 2013) but what is still missing is

a systematic longitudinal investigation of such across-modality relationships underlying associative memory.

The Effect of Task Instructions on Associative Memory

So far, the main observations from studies I and IV involved brain correlates indicating a relatively greater contribution of strategic processes to individual differences in associative memory in older adults and of binding processes in younger adults. If individual differences in associative memory in aging primarily stem from the ability to initiate and apply a strategy, then these differences should become magnified when older adults are asked to intentionally encode associations. That is, knowledge of a subsequent recognition task should primarily benefit those that know how to improve their memory performance. Until today, the effect of task instruction on associative memory has gained little attention in younger and older adults alike. If and how different encoding instructions generally affect associative-memory performance was investigated in younger adults in addition to studying how encoding instructions affect functional brain correlates (study III). Here, we could demonstrate a modulatory effect of task instruction on associative memory, behaviorally as well as neurally.

Younger adults who received intentional encoding instructions performed better in a subsequent associative-recognition task compared to those who received incidental instructions. We did not find a link between encoding-related functional activity and associative memory. Between-person performance differences in neither condition could be accounted for by differences in encoding activity. This might suggest that encoding processes were rather similar across participants. In line with this notion, encoding strategies were rather homogenous across subjects. That is, most participants in the intentional encoding group applied a deep verbal or visual strategy during encoding to remember object associations, although they were not told to do so or provided with any exemplar strategy. For example, subjects tried to find connections between the objects or generated a story or sentence to semantically relate the objects to each other. Subjects from the incidental encoding group did generally not rely on the use of strategies, as they were unaware of a subsequent recognition task. Hence, younger individuals seemed to show little variation in how they encoded the associative materials – they initiated memory strategies by themselves, which is in line with previous observations (Kirchhoff & Buckner, 2006). Instead, differences in performance could have related more to consolidation or retrieval processes that we did not investigate in study III, but which would be interesting to do in the future

(Duncan et al., 2014; Tompary et al., 2015). Overall, in younger adults intentional as opposed to incidental encoding instructions enhanced associative memory, but it is reasonable to assume that this instructional benefit would be more selective in older adults. More precisely, if a) to perform well in an associative memory task requires the self-initiation of a memory strategy (among other processes), and b) older adults have difficulty to self-initiate memory strategies (Naveh-Benjamin et al., 2009; Hertzog et al., 2013), then older adults who show no difficulty in generating strategies may benefit the most from an intentional encoding instruction. In contrast, an incidental encoding instruction may be beneficial to a wider range of older adults, but only if the experimenter would guide their cognitive operations. In a study by Troyer et al. (2006), older adults received both intentional and incidental instructions to encode face-name associations. In the intentional encoding condition, they were asked to remember the associations for a later memory test. In the incidental condition, they were provided with a link between a name and a face (e.g., the link between a woman's face and the name Ms. Rowe, might be: "A row is a line of things. This person's prominent feature is her teeth: they are in a very straight row."). Their results showed that providing the participants with a link between the two items (i.e., the face and the name) resulted in better memory performance compared to intentional encoding instructions. This finding suggests that, older adults are generally able to employ strategies when guided to do so, even if some older adults do not use strategies when not directed to do so. It would be interesting to investigate the extent to which experimenter-guided cognitive operations increase not only overall performance, but also decrease individual differences in associative memory among older adults.

Apart from behavioral differences, study III provided evidence that the type of instructions younger adults were given affected brain activity during encoding and, in the context of associative memory, modulated hippocampal activity. This aspect of brain-activity modulating task features has been addressed before. That is, along its long axis, i.e., anteriorly to posteriorly, hippocampus shows a functional dissociation with regard to task demands (Poppenk et al., 2013). As such, the posterior part of the hippocampus appears to be more engaged in retrieval-related operations, while its anterior portion is more involved in encoding-related processes (Jackson & Schacter, 2004; Prince et al., 2005; Chua et al., 2007). Importantly, in study III we showed that instructions should be taken into account concerning the role of hippocampus during encoding, especially with regard to its long-axis specialization. Our findings suggested that intent to

remember may trigger a binding process that draws on anterior hippocampus.

Hippocampal activity triggered by intentional encoding instructions might further relate to the use of visual exploration strategies. That is, rodent and human studies show that participants use a specific exploration strategy for visual comparison and discrimination of associative-memory information when intentionally encoding stimuli (Voss & Cohen, 2017). For example, systematic viewing with eye saccades can help to maintain perceptual features of associations to be able to later discriminate intact associations from perceptually similar foils. This strategic viewing is related to hippocampal activity (Voss & Cohen, 2017). Voss et al. (2011) further showed that self-generated (i.e., intentional) in comparison with passive visual exploration predicted better episodic memory in humans. Also, attentional processes might have mediated the effects of task instruction on hippocampal activity. Aly and Turk-Browne (2016) recently found that hippocampal activity was related to the attentional state individuals were in, i.e., hippocampal activity was related to attention being directed toward task-relevant information, which resulted in better memory performance. To conclude, intentional encoding instructions in younger adults might elicit not only the use of elaborate memory strategies, but also affect visual exploration and attentional processes.

Finally, given that task instructions had strong effects on brain activity in the younger adult sample, it is important to keep this task-specific effect in mind when interpreting the gray-matter volume findings from studies I and IV. Specifically, in study I, in which older adults had to intentionally encode item pairs, it is reasonable to assume that the relationship between brain volume and performance might have been different under incidental task instructions. The results might have shifted from prefrontal toward hippocampal gray-matter volume correlates. This is so because, under incidental encoding conditions, the relative contribution of the strategic component to associative memory would likely have decreased. Hence, volume in lateral PFC might not have distinguished between individuals any longer. In contrast, the relative contribution of the associative component might have been more pronounced, and hence a link to hippocampal volume could have been observed. In line with this assumption, Zamboni et al. (2013) reported a positive relationship between hippocampal volume and performance in an incidental object-location test among older adults.

In addition to structural and functional brain correlates of associative memory, we also investigated how neurochemical differences may relate to individual differences in associative memory in aging (study II).

The Role of Dopamine in Associative Memory

In study II, we investigated genetic modulators of episodic memory in older adults and found a positive relationship between beneficial DA receptor genotypes and associative, but not item memory. Not many studies have investigated allelic variants of DA receptor genes and associative memory in humans or animals. As such, the results of study II are probably those that need to be interpreted with most caution. At the same time, our study provides a starting point for future studies to further investigate the potentially selective role of DA in associative compared with item memory.

In study II, we examined the effects of aggregated genetic factors, i.e., we computed a risk score that corresponded to beneficial genotypes of DA-related genes, specifically D1, D2, and D3 receptor genes. The combination of multiple genetic factors into a risk score implies that we cannot draw exact inferences about the specific genetic mechanisms and their contribution to individual differences in associative memory. However, single candidate genes are often not associated with imaging traits or cognitive performance (see Raz et al., 2015). The identification of a single SNP with a small risk effect is not necessarily informative, as we carry so many genotypes that are interacting with each other (Rodriguez-Rodriguez et al., 2013). In line with this polygenic view, in study II none of the single DA polymorphisms or those comprising the Alzheimer's risk score related to item or associative memory. Hence, combining multiple genes into one genetic risk score can be more predictive, and therefore more powerful than assessing the effect of single SNPs (Ferencz et al., 2013; Papenberg et al., 2014). Yet, we have to interpret our findings on a broader level, i.e., how DA receptor density in general (indirectly measured with DA genes) could affect associative memory. Previous studies provide evidence that DA D1 and D2 receptors can affect distinct elements of memory, in particular item and associative memory, to different degrees (Tompary et al., 2015). For example, in a pharmacological rodent study, a D1 receptor antagonist (blocking the binding of DA to D1 receptors) was infused in the perirhinal cortex and led to impaired item memory (object recognition). However, item memory was unaffected when the same D1 antagonist was infused in the hippocampus (Balderas et al., 2013). One the other hand, D1 receptor antagonists have been shown to impair associative memory, when infused in the hippocampus (Bethus et al., 2010). Thus, D1 receptors seem to have effects on both item and associative memory depending on where in the MTL they are active. D2 receptors, however, seem to have more selective effects on associative as opposed to item memory. For example, D2 receptor

density has been implicated in recollection-based memory processes (MacDonald et al., 2009) and especially hippocampus-based episodic memory processes (Nyberg et al., 2016). Also, D2 receptors in hippocampus have been shown to affect frontal lobe functions, such as executive functions (Takahashi et al., 2007). As such, D2 receptors might not only affect local hippocampal functions, but also functions outside this region like the PFC that may be relevant for associative memory. Hence, although D1 receptors seem to affect both item and associative memory in perirhinal cortex and hippocampus, respectively, D2 receptors seem to be selectively linked to processes that are more relevant for associative memory. The DA genetic risk score used in study II entailed the DA D3 receptor gene, which belongs to the D2 family. Thus, the two risk profile groups probably differed mostly with regard to D2-like receptor density, which could account for why the allelic variants had stronger effects on associative than on item memory. However, this is just one potential explanation for our findings and others are conceivable. For example, the DA system interacts with other neurotransmitter systems like the acetylcholine system that has also been implicated in hippocampal-dependent memory processes (Hasselmo, 2006; Easton et al., 2012). Hence, the exact mechanisms through which DA receptor genes differentially affect item and associative memory remain to be further determined.

Contrary to the differential effects of DA-associated genes, genetic risk for Alzheimer's disease (including APOE, PICALM, BIN1, CLU polymorphisms) was associated with decreased item and associative memory, without affecting one more than the other. To date, genetic variants of APOE have primarily been associated with decreases in hippocampal volume, an early neuropathological change that occurs in MCI and Alzheimer's disease (Masdeu et al., 2005). In healthy individuals, however, the effect of APOE on hippocampal volume remains unclear (Raz et al., 2015). Although some studies reported a negative relationship between the APOEε4 variant and hippocampal volume (Chiang et al., 2011; den Heijer et al., 2012), others did not find such an association (Troyer et al., 2012; Ferencz et al., 2013; see also Raz et al., 2015). Similarly, Troyer et al. (2012) found a negative relationship between the APOEε4 variant and associative memory and a negative relationship between the APOEε4 variant and hippocampal volume in individuals with amnestic MCI. Their data suggested that volume of the hippocampus mediated the observed relationship between APOE and associative memory. Importantly, in study II, we included a young-old age group (60 years of age), in which all participants were high functioning cognitively, whereas, as reviewed above, the effect of the APOE

gene on hippocampal volume became apparent only after some degree of cognitive decline. In line with this assertion, study I provided no evidence that hippocampal volume differentiated between older adults with good and poor associative-memory performance. It remains to be determined if genetic variants associated with Alzheimer's disease might affect episodic memory in general at age 60 and only later affect associative more than item memory.

To conclude, DA receptor genes seem to contribute to differences in associative memory, more so than they do to item memory. In the future, it would be interesting to investigate if this effect could be replicated in younger adults, which would speak for an age-invariant general effect of DA on associative memory. Similarly, it would be interesting to examine whether the observed specificity of DA genes on associative memory relates to the composition of the specific receptor genes comprising our score (DRD1, DRD2, DRD3) or would be observable also for other DA receptor genes (e.g., DRD4 and DRD5).

Limitations and Future Directions

In this thesis, we used a variety of behavioral and brain measures that come with certain caveats and limitations that are important to acknowledge and to keep in mind in interpreting the results.

In two studies (studies I and IV), we used structural MRI to investigate how gray-matter volume influences associative-memory functioning. Many neuroimaging studies have used functional MRI to investigate the relationship between brain and cognition. One reason for this might be that – although functional MRI provides only an indirect measure of brain activity – the biological underpinnings of brain volume seem much harder to interpret. That is, the neural basis of brain volume can be related to a variety of factors in the neural infrastructure (e.g., myelination, microvasculature, dendritic arbors, or neuron cell bodies; Sowell et al., 2003; Raz & Rodrigue, 2006). There is no direct evidence to which of these factors smaller or larger gray-matter volume relates in humans, although some attribute decline in gray-matter volume primarily to demyelination (Sowell et al., 2003). Thus, the interpretation of volume-cognition findings in the context of underlying biological mechanisms continues to be a challenge (Raz & Rodrigue, 2006).

Further, the findings of study IV revealed a complex relationship between gray-matter volume in MTL and brain activity in IFG. To assess structure-function covariation, we applied jICA that only few studies to date have used. JICA is, however, a powerful tool to detect systematic inter-subject covariation

between patterns of different brain modalities. The advantage of this method lies in the fact that it assesses mutual information of gray-matter volume and brain activity. In contrast, more commonly used methods such as correlational analysis constrain the analysis of one brain modality by features of another (Sui et al., 2014). Moreover, with individual component loadings, jICA provides a measure that reflects the strength of association between gray-matter volume and activity that can be used for correlations with performance. However, an important remark here is that the observed associations cannot be interpreted in causal terms, not even with regard to the biological plausibility of the direction of the relationship. As such, it remains to be determined exactly how gray-matter volume in hippocampus relates to activity in IFG. Future studies should elucidate the biological underpinnings of such structure-function links. For example, gray-matter volume might not be the only factor affecting activity in a given brain region. Microstructural integrity or molecular modifications could potentially explain BOLD signal changes in distinct brain regions (Kalpouzos et al., 2012). Even though the findings of study IV are not straightforward with regard to their interpretation, methods like ICA are still useful to understand complex network properties of the brain.

In study II, we observed that DA-relevant genetic variants modulate memory performance. When investigating genetic effects, it is important to keep in mind that genes modulate the brain and the brain modulates cognition. This also implies a huge gap between genes and cognition, i.e., there is a variety of factors that could mediate the observed relationship between the variables of interest. Genetic variations can, for example, affect proteins in a cell, synaptic plasticity, and entire neural circuits. For example, DA has been shown to influence cerebral vasculature responsivity (Palmer, 1986) and might therefore have an indirect effect on structural brain integrity (Raz & Rodrigue, 2006). Future studies should investigate the linkage between DA receptor genes and gray-matter volume, which could further elucidate the relation between DA and individual differences in associative memory.

Finally, in this thesis we aimed to investigate inter-individual differences in associative memory and their neural correlates. However, the exact nature of the processes that relate to the observed neural correlates, their interactions and the extent to which they underlie performance differences, remain unanswered. Moreover, the mechanisms behind associative success or failure can be diverse and even within a person might differ from one test trial to another. Although we investigated relatively homogeneous age groups in all four studies, there might still be

reasons for differences in associative-memory performance that might not be generalizable across all individuals. Future studies should investigate the specificity of cognitive processes that underlie differences in associative memory (Devitt & Schacter, 2016) as well as the precise role of neural networks therein. This could be done by modulating individuals' cognitive operations when they perform an associative-memory task while investigating the neural correlates of such operations.

CONCLUDING REMARKS

In this thesis, we aimed to further our understanding of what underlies individual differences in associative memory, with a specific focus on structural, functional, and neurochemical differences in the brain. Across two studies, we demonstrated that hippocampal and lateral PFC volume differentially contribute to associative memory in younger and older adults, respectively. This speaks for different associative and strategic operations underlying successful associative memory in these age groups. Yet, a direct age comparison is needed in future studies to further strengthen the interpretation of our findings. Moreover, associative-memory performance is dependent on the type of encoding instruction, as demonstrated in another study. Here, we also received further support for the notion of a relative stronger contribution of binding in comparison to strategic processes distinguishing between younger adults with regard to associative memory. However, hippocampal and PFC contributions should not be thought of as separate entities, as a strong structural-functional coupling between the two is critical for successful associative memory. Finally, differences in associative memory go beyond gray-matter volume and brain activity, and extend to neurotransmitter systems. Especially DA D2 receptors seem to be relevant for associative-memory functioning. The relationship between DA, gray-matter volume, and brain activity and their combined contribution to associative memory should be further established in future studies. Thus, brain factors that underlie associative memory are many-faceted and vary as a function of age and task-specific features.

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